Researchers discover new way to kill pediatric brain tumors

February 9 2010

Researchers at Washington University School of Medicine in St. Louis have shown once again that "ready, fire, aim," nonsensical though it may sound, can be an essential approach to research.

The scientists robotically "fired" 2,000 compounds into culture plates containing tumor cells to see if the compounds had any effect. When the robotic screener found one substance had scored a hit by inhibiting growth of the tumor cells in its plate, researchers analyzed what that compound acted against. Follow-up studies showed that the drug slowed tumor growth in mice by inhibiting the function of a protein called STAT3.

As a result, researchers now have a previously unrecognized target, STAT3, at which they can "aim" new drugs for the treatment of cancer in neurofibromatosis-1 (NF1), a genetic condition that causes increased risk of benign and malignant brain tumors.

"We were excited to find that the slowed tumor growth we observed following treatment resulted from increased tumor cell death — an effect we hadn't seen before when we blocked other NF1 growth control molecules," says senior author David H. Gutmann, M.D., Ph.D., the Donald O. Schnuck Family Professor of Neurology. "Now we can identify the genes that STAT3 influences to fine-tune our treatments and ensure that we kill cancer cells with minimal harm to normal cells."

Gutmann is director of the Neurofibromatosis Center at Washington

University, a national referral center for patients with all forms of neurofibromatosis. The center is active both in clinical trials and in basic research to help develop innovative new approaches for treating patients with NF. Gutmann is also co-director of the neuro-oncology program at the Siteman Cancer Center at Washington University School of Medicine and Barnes-Jewish Hospital.

Gutmann collaborated on this project with David Piwnica-Worms, M.D., Ph.D., professor of radiology and of developmental biology and director of the Molecular Imaging Center at Washington University. The results appear this month in the journal *Cancer Research*.

Cucurbitacin-I, the compound that led scientists to STAT3, is a plant steroid. It belongs to a family of bitter-tasting compounds previously identified as inhibitors of STAT3. Gutmann says cucurbitacin-I is likely too toxic to be suitable for use in clinical trials at this time.

After the successful robotic test of cucurbitacin-I, researchers showed that STAT3, which turns on and off the activity of a number of genes, is unusually active in NF1 tumor cells. Further investigation revealed that STAT3 activity is regulated by another gene very familiar to Gutmann: the mammalian target of rapamycin (mTOR).

Gutmann's laboratory linked mTOR and the processes it controls to NF1 years ago. The new connection between STAT3 and the mTOR pathway makes STAT3 the last link in a chain of molecules that take growth-promoting signals from the cell membrane to the nucleus. Gutmann says he is encouraged by the possibility that scientists might be able to decipher the genetic program controlled by STAT3 in order to develop more refined treatments for tumors in patients with NF1.

"We went in with a 'we don't know enough' approach, let's try 'ready, fire, aim,' and it paid off," he says.

More information: Banerjee S, Byrd JN, Gianino SM, Harpstrite SE, Rodriguez FJ, Tuskan RG, Reilly KM, Piwnica-Worms DR, Gutmann DH. "Neurofibromin controls cell growth by regulating signal transducer and activator of transcription 3 activity in vitro and in vivo." Cancer Research, Feb. 15, 2010.

Provided by Washington University School of Medicine